REMARKS

In response to the Office Action mailed March 30, 2009 ("Office Action"), Applicants respectfully request reconsideration in view of the following remarks. Claim 2 is cancelled and claim 13 is withdrawn, claims 1, 4, 5 and 7 are currently amended, therefore claims 1 and 3-12 remain pending. No new matter has been introduced.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO96/13499 (Published May 9, 1996; Provided by Applicants) in view of United States Patent Publication 2002/0147201 (Published October 10, 2002) and Basit et al. (The Effect of Polyehtylene Glycol 400 on Gastrointestinal Transit: Implications for the Formation of Poorly Water Soluble Drugs, Pharmaceutical Research, Volume 18, No. 8, 2001).

Particularly, the Office Action alleges, *inter alia*, "with regard to Claim 1, WO 96/13499 teaches an oral solution comprising 1mg/ml of mitratapide (Page 17, Compound No. 22), a solvent (Page 26, Example 8), and sucrose as a taste modifying agent (Page 26, Example 8). Additional ingredients may be included to aid in the solubility of mitratapide (Page 10, Line 18)." Moreover, it is stated that "WO 96/13499 does not teach the incorporation of an antioxidant or specific compounds which will increase the solubility of the mitratapide active agent."

The aforementioned rejection is respectfully traversed. Applicants respectfully disagree with the Office Action regarding the aforementioned rejection. First, with respect to the Office Action's allegation that WO-96/13499 teaches an oral solution comprising mitratapide and a solvent (page 26, example 8). It should be noted that said Example 8 on page 26 teaches an aqueous solution, not an oral solution. Second, the Office Action alleges on page 4 (third paragraph from the bottom) "Additional ingredients may be included to aid in the solubility of mitratapide (page 10, line 18)." However, the complete sentence starting on page 10, line 16, of WO-96/13499 reads "For *parenteral* compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included." Again this sentence teaches that for aqueous solutions comprising mitratapide other ingredients may be added to aid solubility. The present

invention is an oral solution, not an aqueous soloution. Accordingly, the present invention cannot be obvious in view of WO96/13499 in view of United States Patent Publication 2002/0147201 and Basit et al.

The Office Action also alleges, *intera alia*, "However, US 2002/0147201 teaches a means for increasing the solubility of active agents (Abstract). One way to increase active agent solubility is to add a plasticizer such a polyethylene glycol (PEG) to the composition (Paragraph 64). After achieving the desired solution, it is important to keep the solution from degrading in any way. Commonly, the butylated hydroxyanisole (BHA), an antioxidant is used at 0-15% by weight to stabilize a composition (Paragraph 76). If the composition is for oral adminstration, it should have a preferable taste. Taste modifying agents are commonly employed for this purpose and may be in the form of sweeteners such as sucrose or sucralose at 0 to 10% by weight (Paragraph 61)."

The aforementioned rejection is respectfully traversed. Applicants respectfully disagree with the Office Action regarding the aforementioned characterization of US-2002/0147201. First, the Office Action states (bottom of page 4) "US-2002/0147201 teaches that one way to increase active agent solubility is to add plasticizer such as polyethylene glycol (PEG) to the composition (paragraph 64 of US-2002/0147201)." This is repeated on page 5 of the Office action in the second to last paragraph.

The Applicants point out, however, that said §64 in US-2002/0147201 has to be read in conjunction with §58:

> § 58: "In addition to the active agent and glycyrrhizin that dosage forms may incorporate additional ingredients. These additional ingredients include, for example, preservatives, chelating agents, surfactants, taste modifiers, buffering agents, antacids, plasticizers, water soluble fillers, water insoluble fillers, binders, glidants, film formers, enteric coatings, solvents, coloring agents, thickening agents, osmotic agents, and semi-permeable membrane-forming agents."
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> §64: "Plasticizers include glycerin, sorbitol, propylene glycol, polyethylene glycol, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters. Preferable, the dosage forms of the present invention can include 0 to 40% plasticizers on a weight basis."

- Nowhere in the paragraphs 58 and 64 is it mentioned that plasticizers in general, or polyethylene glycol in particular, are added in order to increase the solubility of the active ingredient. Plasticizers in general, or polyethylene glycol in particular, are cited as "additional ingredients" but their specific purpose is nowhere mentioned in US-2002/0147201. As defined in Wikipedia, "Plasticizers or dispersants are additives that increase the plasticity or fluidity of the material to which they are added ...". Accordingly, US-2002/0147201 does not teach the skilled person the incorporation of polyethylene glycol in order to increase the solubility.
- In addition, it should be noted that US-2002/0147201 in general teaches a means for increasing the solubility and bioavailability of active ingredients by forming a complex of said active ingredients with glycyrrhizin. (*See* e.g., paragraph 19 and 45.) Furthermore, US-2002/0147201 teaches that these complexes (from active ingredient and glycyrrhizin) are highly water-soluble. If the skilled person would have followed the teaching of US-2002/0147201, the artisan would have made complexes of mitratapide with glycyrrhizin. The present invention however does NOT make use of glycyrrhizin.

Furthermore, it should be stressed that the mitratapide solutions of the present invention are <u>not aqueous</u> solutions but use an <u>organic solvent</u>. In view of this point, Applicant's have amended claim 1 to include the subject matter of claim 2, thereby providing further clarity of the organic solvents in claim 1.

The Office Action also alleges, *intera alia*, "Basit teaches that PEG 400 is a particularly preferred solubility enhancer for poorly water-soluble drugs because in addition to its superior ability to increase the solubility of such drugs, PEG 400 concurrently reduces gastrointestinal transit time (Page 1149, Column 2). Therefore, PEG 400 is not only an inert pharmaceutical excipient (Page 1149, Column 2), but also has an effect on the bioavailability of the co-administered drug (Page 1149, Column 2)."

Applicants respectfully disagree with the Office Action regarding the aforementioned allegations. As mentioned above, if the skilled person would have started from the teaching of WO-96/13499 and would have combined it with the teaching of US-2002/0147201 then the skilled person would have ended up with an aqueous solution of mitratapide complexed with glycyrrhizin. As explained in paragraph 0008 of the present application due to the very limited solubility of

mitratapide in water, the skilled person would not look into the development of aqueous solutions and would not combine the teaching of WO-96/13499 with US-2002/0147201. In the absence of the combined teaching of WO-96/13499 with US-2002/0147201, the Basit et al. reference stands on its own and there is no motivation to combine WO-96/13499 with the Basit et al. reference.

Finally, the Office Action states, *inter alia*, "It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to be motivated to combine the teachings of WO 96/13499 with US 2002/0147201 and Basit because WO 96/13499 teaches the additional ingredients which increase the solubility of mitratapide are preferable, US 2002/0147201 teaches methods of increasing solubility and bioavailability of an active drug including that incorporation of PEG into the composition, and Basit specifies that PEG 400 has unique preferable qualities over other solubility enhancing agents."

Again, Applicants respectfully disagree with the Office Action regarding the aforementioned statement. The teaching of WO-96/13499 is directed to aqueous solutions comprising mitratapide. The teaching of US-2002/0147201 is directed to a means for increasing the solubility and bioavailability of active ingredients by forming a complex of said active ingredients with glycyrrhizin. If the skilled person would have started from the teaching of WO-96/13499 and would have combined it with the teaching of US-2002/0147201 then the skilled person would have ended up with an aqueous solution of mitratapide complexed with glycyrrhizin. Since the present invention is a non-aqueous solutions of mitratapide in an organic solvent, this is very different than what would have been done by the skilled person when following the teaching of WO-96/13499 and US-2002/0147201. Further, there is no motivation to combine WO-96/13499 with the Basit et al. reference. Accordingly, the applicants respectfully submit that the claimed compounds are not prima facie obvious over WO96/13499 in view of United States Patent Publication 2002/0147201 and Basit et al. Thus, applicants request withdrawal of the rejection under 35 U.S.C. §103(a).

Please charge any fees, which may be required for this submission to Johnson & Johnson Deposit Account 10-0750/PRD2166USPCT/JKM.

Applicant respectfully requests that early action be taken in this case.

Respectfully submitted,

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